AstraZeneca

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **ROBERTS ET AL.**	Filed: **November 17, 2003**
Application No: **10/714,447**	Attorney Docket No.: A1479-3P US
Art Unit: **1624**	Examiner: **Emily Bernhardt**
Title: **Novel Compounds with Analgesic Effects**	

MAIL STOP **APPEAL BRIEF-PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF PURSUANT TO 37 CFR 41.37

(1) REAL PARTY IN INTEREST

The real party in interest in this appeal is AstraZeneca Canada Inc. having a principal place of business at 1004 Middlegate road, Mississauga, Ontario L4Y 1M4, Canada. AstraZeneca Canada Inc. is the assignee and owner of the entire interest in the above identified application by virtue of a series of assignments recorded in the United States Patent and Trademark Office on 1) April 24, 1997 at Reel/Frame 9531/0722, 2) September 24, 1998 at Reel/Frame 9232/0471, and 3) October 12, 2000 at Reel/Frame 011217/0591.

(2) RELATED APPEALS AND INTERFERENCES

The undersigned knows of no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) STATUS OF THE CLAIMS

Claim 19 stands rejected and is the subject of this appeal.

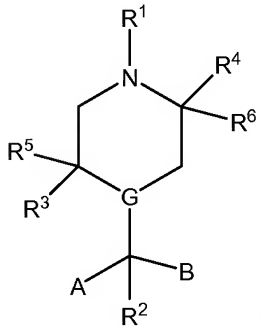
Claims 1-18 have been canceled.

(4) STATUS OF AMENDMENTS FILED SUBSEQUENT TO THE FINAL REJECTION

There have been no amendments filed subsequent to the Final rejection mailed February 16, 2006.

(5) SUMMARY OF THE CLAIMED SUBJECT MATTER

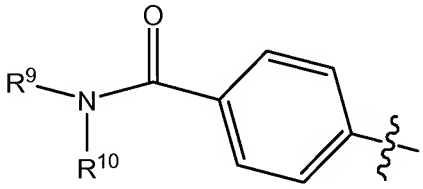
The claimed subject matter that forms the basis of this appeal is directed to piperazinyl compounds useful for binding to delta opioid receptors and treating pain represented by formula (I)



(I)

wherein G is a nitrogen atom;

A is:



wherein the phenyl ring of the A group is optionally substituted by one or two substituents independently selected from the group consisting of CH_3, CF_3 and halogen;

R^1 is selected from the group consisting of: H; a branched or straight C_1–C_6 alkyl; –$CO(C_1$–C_6 alkyl); and (C_1–C_6 alkyl)-B' wherein B' is a C_6, C_9 or C_{10} aryl or a 5 or 6 membered heteroaryl having a heteroatom selected from any of S, N and O and wherein the C_6, C_9 or C_{10} aryl and the 5 or 6 membered heteroaryl are optionally substituted with 1 or 2 substituents selected from CH_3 or halogen;

R^2 is selected from the group consisting of H and CH_3;

R^9, and R^{10}, are selected from the group consisting of H, a branched or straight C_1–C_6 alkyl and a C_2–C_6 alkenyl;

B is an C_6, C_9 or C_{10} aromatic; or a C_6, C_9 or C_{10} hydroaromatic; each being optionally substituted by 1 or 2 substituents independently selected from CH_3, CF_3,

halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, OR^7, $(CH_2)_pSOR^7$, $(CH_2)_pSO_2R^7$ and $(CH_2)_pSO_2NR^7R^8$;

wherein p is 0, 1, or 2, and wherein R^7 and R^8 are selected from: H; a branched or straight C_1–C_6 alkyl; or –CO(C_1–C_6 alkyl); and

R^3, R^4, R^5, and R^6 are each H;

as well as pharmaceutically acceptable salts, hydrates, isoforms and isomers, other than positional isomers, thereof.

(6) GROUNDS OF REJECTION PRESENTED FOR REVIEW

a. 35 U.S.C. § 103(a)

Claim 19 stands rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Calderon and Bilsky References in view of Chang et al. (PCT Publication WO93/15062 or U.S. Pat. No. 5,658,908, applied as of its § 102(e) date).

(7) ARGUMENTS

The Examiner's rejection under § 103(a) is improper because the Chang et al. and Calderon references expressly teach away from Applicants' claimed invention and therefore there is no motivation to combine the Calderon and Bilsky references with Chang et al so as to arrive at Applicants' claimed invention.

The full citations for the Calderon and Bilsky References are set forth in Appendix D submitted herewith. The Calderon and Bilsky references were cited as C1, C2, C4, and C5 in the Information Disclosure Statement submitted by Applicants on November 17, 2003.

In the March 22, 2005 final office action, the Examiner asserted that the claim 19 formula (I) compounds were obvious over Calderon et al. and Bilsky et al. in view of Chang et al. because hydrogen and methyl on the piperazino carbons are taught as interchangeable in similar compounds having the same use as described by Chang et al. That is, the Examiner asserted that the compounds claimed in accordance with formula (I) of claim 19 were obvious variants over the primary references.

The Calderon and Bilsky references, however, only disclose compounds with dimethyl groups on the central piperazine ring. In fact, all of the examples disclosed in all four of the Calderon and Bilsky references contain dimethyl groups on the central piperazine rings. The inclusion of examples directed only to compounds containing dimethyl substituted piperazinyl rings evidences the importance Bilsky et al. and Calderon et al. placed on having a dimethyl substituted central piperazinyl ring. Furthermore, under the heading "Chemistry" at page 696 in the Calderon reference identified as C5 in Applicants' IDS, Calderon et al. expressly emphasized the importance of using a dimethyl substituted intermediate, which is chiral due to the dimethyl substitution, in synthesizing the dimethyl substituted final product. Had there not been a dimethyl group on the piperazine ring, the intermediate used in the Calderon reference would have been achiral and the resulting products would not have been readily separable and optically pure.

In contrast, claim 19 of Applicants claimed invention is directed to compounds containing an unsubstituted central piperazine ring, wherein Claim 19 defines the R^3, R^4, R^5, and R^6 substituent groups of formula (I) so as to limit such groups to hydrogen.

The Examiner, however, is proposing that Calderon et al. be combined with Chang et al. to eliminate the dimethyl substitution Calderon et al. expressly identifies as a key advantage to the dimethyl substituted compounds described therein. Indeed, the Examiner is proposing such a combination in the face of Calderon et al.'s express statements indicating the import of the dimethyl substitution. As a result, Applicants respectfully assert that Calderon et al. expressly teaches away from Applicant's claimed invention and the combination with Chang et. al. proposed by the Examiner. Accordingly, Applicants respectfully submit there is no motivation to combine the Calderon and Bilsky references with Chang et al. in the manner proposed by the Examiner. In view of the foregoing, Applicants respectfully assert that claim 19 is not obvious over Calderon et al. and Bilsky et al. in view of Chang et al.

Applicants further submit that claim 19 is not obvious over the Calderon and Bilsky references in view of Chang et al. because Chang et al expressly teaches away from claim 19. A prior art that teaches away from a claimed invention is a significant factor to be considered in determining obviousness. MPEP §2146.1. References cannot be combined where references teach away from their combination. MPEP §2146.2. In addition, a prior art reference must be considered in its entirety, including disclosures that teach away from the claims. MPEP §2141.02

In the case at hand, Chang et al. teaches it is important to have a dimethyl substituted piperazine ring to achieve the desired opioid activity. More specifically, Chang et al. stated in in relevant part in reliance on a 132 declaration submitted concurrently therewith as follows:

> Specifically, these tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II, had no substituents on carbon atoms of the piperazine ring. The other compound of the pair was the same as the first, except that it had two methyl groups on carbon atoms of the piperazine ring. The test results, comparing compounds in which the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, *show a general trend in which the substituted compounds have significantly greater opioid activity*. (Emphasis added).

(See page 60 of the February 9, 1996 response attached hereto as Appendix B and made of record in Applicants' November 30, 2005 response.) The file wrapper of Chang et al. is considered an integrated part of Chang. A person of ordinary skill in the art in reading Chang et al. as a whole would not be motivated to combine Chang et al. and Calderon and Bilsky references in the manner needed to arrive at Applicants' claimed invention. Rather, a person of ordinary skill in the art upon viewing Chang et al. in its entirety would be motivated to retain the methyl groups on the piperazine ring as specifically taught by Chang et al. As a result, a person of ordinary skill in the art would not be motivated to combine Chang et al. and the Calderon and Bilsky references so as to arrive at Applicants' claimed invention. Accordingly, Applicants respectfully assert that claim 19 is not obvious over Calderon et al. and Bilsky et al. in view of Chang et al.

Applicants further submit that there is no motivation in the prior art to modify Chang et al. so as to arrive at the presently claimed invention.

Indeed, a person of ordinary skill in the art upon reading Chang et al. as a whole would be led to believe that optimal delta receptor binding activity is only achieved when the central piperazine ring is substituted, and thus, would not be motivated to modify Chang et al. to arrive at the presently claimed invention, which contains no substitution on the piperazine ring, by removing the methyl groups of Chang et al. In fact, Chang et al. indicates over and over throughout the specification that his preferred compounds have at least one methyl group attached to at least one carbon group of the piperazinyl ring. (See, page 8; page 10; page 11; Table I, page 26; Table II, page 28; page 32; page 34; page 36; Table III, page 37; page 38; page 39; and Table IV, pages 39-40 of WO WO93/15062). Moreover, all of the Example 1-50,

53-76, and 78-91 piperazinyls are substituted on the piperazinyl ring with 2 or more methyl groups. Specifically, Examples 1-11, 14-33, 35-38, and 40-91 contain a dimethyl substituted piperazinyl ring, while Examples 12, 13, 34, and 39 contain a trimethyl substituted piperazinyl ring. Please note, Examples 51, 52, and 77 contain piperidinyl—not piperazinyls—rings. Moreover, the "particularly preferred compounds" of Chang et al. (See page 25 of WO WO93/15062) all have a dimethyl substituted piperazinyl ring. Furthermore, Chang et al. indicates numerous times throughout that the specification that the preferred compounds (col. 6 of U.S. Pat. No. 5,658,908) require at least one of R^3, R^4 and R^5 to be methyl to bind to delta opioid receptors (see also ln. 38, col.5; ln. 54-55, col. 6; ln.14, col.7; ln. 52, col. 19; ln. 15, col. 22; ln. 10, col. 24; and claim 1 of Chang et al). It would be reasonable in view of the aforementioned for a person of ordinary skill in the art to believe it is critical to have one or more methyl groups substituted on the piperazine ring to achieve the desired delta receptor binding activity. In contrast, compounds of the instant claim 19 do not contain any methyl groups on the central piperazine ring. As a result, an ordinary person of skill in the art upon reading Chang et al would not be motivated to modify Chang et al. so as to arrive at the presently claimed invention. Accordingly, Applicants respectfully assert that claim 19 is not obvious over Calderon et al. and Bilsky et al. in view of Chang et al.

In summary, Applicants respectfully submit that the Office made clear errors and/or omitted one or more essential elements needed to establish a *prima facie* rejection and reversal of the rejection is respectfully requested.

Respectfully submitted,

Respectfully submitted,

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/Jacqueline M. Cohen/

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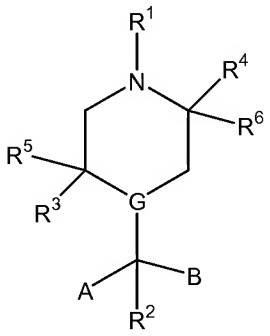
Dated: June 25, 2007
Reg. No: 51,574

APPENDIX A
COPPY OF CLAIM INVOLVED IN APPEAL

Claims 1-18. (Cancelled).

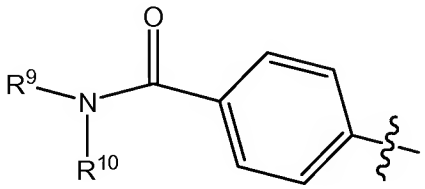
19. A compound of formula (I)



(I)

wherein G is a nitrogen atom;

A is:



wherein the phenyl ring of the A group is optionally substituted by one or two substituents independently selected from the group consisting of CH_3, CF_3 and halogen;

R^1 is selected from the group consisting of: H; a branched or straight C_1–C_6 alkyl; –CO(C_1–C_6 alkyl); and (C_1–C_6 alkyl)-B' wherein B' is a C_6, C_9 or C_{10} aryl or a 5 or 6 membered heteroaryl having a heteroatom selected from any of S, N and O and wherein the C_6, C_9 or C_{10} aryl and the 5 or 6 membered heteroaryl are optionally substituted with 1 or 2 substituents selected from CH_3 or halogen;

R^2 is selected from the group consisting of H and CH_3;

R^9, and R^{10}, are selected from the group consisting of H, a branched or straight C_1–C_6 alkyl and a C_2–C_6 alkenyl;

B is an C_6, C_9 or C_{10} aromatic; or a C_6, C_9 or C_{10} hydroaromatic; each being optionally substituted by 1 or 2 substituents independently selected from CH_3, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, OR^7, $(CH_2)_pSOR^7$, $(CH_2)_pSO_2R^7$ and $(CH_2)_pSO_2NR^7R^8$;

wherein p is 0, 1, or 2, and wherein R^7 and R^8 are selected from: H; a branched or straight C_1–C_6 alkyl; or –CO(C_1–C_6 alkyl);

R^3, R^4, R^5, and R^6 are each H;

as well as pharmaceutically acceptable salts, hydrates, isoforms and isomers, other than positional isomers, thereof.

APPENDIX B
EVIDENCE APPENDIX

Please see comments made in Chang et al.'s February 9, 1996 response attached hereto. These pages were made of record in Applicants' November 30, 2005 response.

Appendix I

Patent Application
3022-107

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kwen-Jen CHANG, et al.

Group Art Unit: 1202

Application No. 08/284,445

Examiner: E. Bernhardt

Date Filed: August 3, 1994

For: **"OPIOID DIARYLMETHYLPIPERAZINES AND PIPERIDINES"**

EXPRESS MAIL CERTIFICATE

It hereby is certified by the person identified below that this paper is being mailed by such person to the Commissioner of Patents and Trademarks on the date specified, in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231, and Express Mailed under the provisions of 37 CFR 1.10.

Mary B. Caruso
Signature

MARY B. CARUSO
Name of Person Mailing This Paper

FEBRUARY 9, 1996
Date of Mailing

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AMENDMENT RESPONDING TO AUGUST 9, 1995 OFFICE ACTION IN U.S. PATENT APPLICATION NO. 08/284,445

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the 9 August 1995 Office Action in the above-identified application, please amend the application, as follows:

In the Claims

Amend the claims as follows:

The Examiner has requested the month of publication for references BD-BH, which are as follows. BD: November, 1993; BE: October, 1993; BF: November, 1993; BG: November, 1993; BH: November, 1993.

Claims 1-8, 12-14, 38-40 and 44 were rejected in the 9 August 1995 Office Action as being drawn to improper Markush group(s) on the basis that the variables G, R^9 and R^{10} embrace more than one invention as discussed in the restriction requirement.

In the restriction requirement dated April 5, 1995, the Examiner sought to limit claim 1 to G=N and exclude R^9 and R^{10} from being C_3 and higher. Applicants respectfully disagree with this suggestion, particularly since the claims have already been examined on the merits. Furthermore, according to M.P.E.P. Section 803,

> "[i]f the search and examination of an entire application can be made without serious burden, the examiner **must** examine it on the merits, even though it includes claims to distinct or independent inventions."

Thus, since examination on the merits has already occurred, it is clear that the Markush groups of the claims are in proper form according to the M.P.E.P.

For the foregoing reasons, the Section 112 rejections have been overcome, as described in the above discussion, and through the foregoing amendments, which serve to clarify claims 1, 5, 7, 12, 14-17, 38 and 44.

Arguments for Patentability

As discussed above, references AM, AS-AU and BD-BH do not qualify as prior art.

Claims 1, 3, 14-17 and 38-40 were rejected in the 9 August 1995 Office Action under 35 U.S.C. Section 102(b) over references AW and AY. Furthermore, claims 20, 21 and 24 were rejected in the 9 August 1995 Office Action under 35 U.S.C. Section 103 over references AW and AY.

AW and AY are directed to a calcium antagonist, KB-2796, which is I-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride. Related compounds A, B, C, Flunarazine and Cinnarizine are also discussed. (See the structural configurations in AW, Figure 1 and AY, Table 1.) None of the compounds discussed in AW or AY teach or suggest the compounds of the present invention.

Instead, the present invention, as claimed, is related to opioid diarylmethylpiperazines and piperidines. The claims of the present invention, as amended, are directed to diarylmethylpiperazines and piperidines having a particular type of substituent attached to at least one of the carbon atoms in the piperazine ring. For example, according to claim 1, as amended, the substituents on the piperazine are as follows:

> "R^3, R^4 and R^5 may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R^3, R^4 or R^5 is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R^3, R^4 and R^5 together may form a bridge of 1 to 3 carbon atoms."

In contrast, AW and AY do not teach or suggest such compounds having a substituent attached to at least one of the carbon atoms in the piperazine ring.

132?

According to the enclosed Declaration under 37 C.F.R. 1.131 by Dr. Robert McNutt, comparisons have been made between compounds that have a substituent attached to at least one of the carbon atoms in the piperazine ring and those that do not, using the assay procedures set out in Example 92 on pages 156-157 of the specification.

Specifically, these tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II, had no substituents on carbon atoms of the piperazine ring. The other compound of the pair was the same as the first, except that it had two methyl groups on carbon atoms of the piperazine ring. The test results, comparing compounds in which the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, show a general trend in which the substituted compounds have significantly greater opioid activity.

The compounds tested were as follows, wherein Compounds 1-4 have no substituents on carbon atoms of the piperazine ring, and Compounds 1a-4a have two methyl groups on carbon atoms of the piperazine ring:

Compound 1: (+)-3-(-‡-(4-Allyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 1a: (+)-3-((‡R*)-‡-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 2: (+)-3-(‡-(4-Allyl-1-piperazinyl)-4-bromobenzyl)phenol;

Compound 2a: (+)-3-((‡R*)-‡-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-bromobenzyl)phenol;

Compound 3: (+)-3-(‡-(4-Allyl-1-piperazinyl)benzyl)phenol;

Compound 3a: (+)-3-((‡R*)-‡-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

Compound 4: (+)-3-(‡-(4-Methyl-1-piperazinyl)benzyl)phenol; and

Compound 4a: (+)-3-((‡R*)-‡-((2R*,5S*)-2,4,5-Trimethyl-1-piperazinyl)benzyl)phenol.

The compounds having methyl groups on the piperazine ring can be found in the present specification as follows. Compound 1a can be found, for example, on page 12, number 1. Compound 2a can be found, for example, on page 14, number 40. Compound 3a can be found, for example, on page 15, number 47. Compound 4a can be found, for example, on page 21, number 136.

The test results for Compounds 1-4 and Compound 1a-4a using assays described in Example 92 on pages 156-157 of the specification are as follows:

Compound	Mu Receptor IC50 (nM)	Mouse Vas Deferens ED50 (nM)	Delta Receptor IC50 (nM)
Compound 1	3500	2000	50
Compound 1a	90	40	15
Compound 2	2000	*	60
Compound 2a	200	100	80
Compound 3	200	nd	60
Compound 3a	25	78	1.3
Compound 4	700	nd	140
Compound 4a	1.6	46	38

nd = not determined

* Test results showed that Compound 2 has antagonist activity rather than agonist activity in the mouse vas deferens assay

According to Dr. McNutt's Declaration, the test results show that substituted Compound 1a has fifty times more potency than unsubstituted Compound 1 according to the Mouse Vas Deferens ED50, more than thirty times more potency according to the Mu Receptor IC50, and more than three times more potency according to the Delta Receptor IC50. Substituted Compound 2a has ten times more potency than Compound 2 according to the Mu Receptor IC50. Substituted Compound 3a has more than 45 times more potency than unsubstituted Compound 3 according to the Delta Receptor IC50 and 8 times more potency according to the Mu Receptor IC50. Compound 4a has more than four hundred times more potency than unsubstituted Compound 4 according to the Mu Receptor IC50 and more than three times more potency according to the Delta Receptor IC50.

Thus, the test results comparing compounds in which the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, show a general trend in which the substituted compounds have significantly greater opioid activity according to test results of assays described in Example 92 on pages 156-157 of the specification. This general trend was an unexpected result of the addition of a substituent on the piperazine ring, which is not taught or suggested by the calcium antagonists disclosed in references AW or AY, taken alone or in combination.

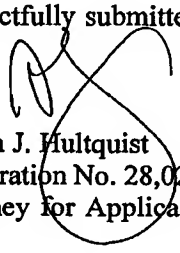
Thus, references AW and AY do not teach or suggest the compounds of the present invention, as claimed, which is directed to opioid diarylmethylpiperazines and piperidines in which there is a substituent attached to at least one of the carbon atoms in the piperazine ring.

Applicants note for the record that claims 4-8, 12, 13, 18, 19, 23, 25-28, 44, 64 and 65 have been found patentable over the prior art, particularly since AS-AU, BD-BH and AM do not qualify as prior art as discussed above.

For all of the foregoing reasons, claims 1, 3-8, 12-21, 23-28, 38-40, 44, 64 and 65, as amended, are fully patentably distinguished over the references cited and are in condition for allowance.

If any issues remain outstanding in connection with the allowance of this application, the Examiner is requested to contact the undersigned attorney, at (919) 990-9531 to discuss their resolution, so that this application can be passed to issue at an early date, consistent with the substantial advance in the art achieved by the invention claimed in this application.

Respectfully submitted,



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Patent Application
3022-107

#10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kwen-Jen CHANG, et al. Group Art Unit: 1202

Application No. 08/284,445 Examiner: E. Bernhardt

Date Filed: August 3, 1994

For: **"OPIOID DIARYLMETHYLPIPERAZINES AND PIPERIDINES"**

EXPRESS MAIL CERTIFICATE

It hereby is certified by the person identified below that this paper is being mailed by such person to the Commissioner of Patents and Trademarks on the date specified, in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231, and Express Mailed under the provisions of 37 CFR 1.10.

Mary B. Caruso
Signature

MARY B. CARUSO
Name of Person Mailing This Paper

FEBRUARY 9, 1996
Date of Mailing

EG561244813US
Express Mail Label Number

DECLARATION OF DR. ROBERT MCNUTT
UNDER 37 C.F.R. Section 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Robert Walton McNutt, Jr., hereby declare and state the following:

1. I am a citizen of the United States of America, residing at 700 Morreene Road, Durham, NC 27705, and hold a Ph.D. in organic chemistry from Boston College, granted in 1977, and I have been employed by Burroughs Wellcome, now Glaxo Wellcome, since 1979 and continuing to date, currently holding the position of Research Scientist in such company.

2. I am an inventor of subject matter described and claimed in United States Patent Application Serial No. 08/284,445 filed 03 August 1994 in the names of Kwen-Jen Chang, Grady Evan Boswell, Dulce Garrido Bubacz, Mark Allan Collins, Ann Otstot Davis, and Robert Walton McNutt, Jr. (and hereinafter referred to as the "Application").

3. I am aware that the United States Patent and Trademark Office has issued an Office Action dated 09 August 1995 in the Application, and that in such Office Action, among other rejections, claims 1, 3, 14-17 and 38-40 were rejected under 35 U.S.C. Section 102(b) as anticipated by references AW and AY, and claims 20, 21 and 24 were rejected as obvious in view of references AW and AY. References AW and AY are as follows:

AW Iwamoto et al., "Calcium Antagonism by KB-2796, a New Diphenylpiperazine Analogue, in Dog Vascular Smooth Muscle," J. Pharm. Pharmacol. 43, 535-539, 1991 ("Iwamoto I"); and

AY Iwamoto et al., "Effects of KB-2796, a New Calcium Antagonist, and Other Diphenylpiperazines on [3H]Nitrendipine Binding," J. Pharmacol., 48, 241-247 (1988) ("Iwamoto II").

4. I have read and am familiar with the references identified in Paragraph 3 above.

5. The references identified in Paragraph 3 above disclose the following compounds:

"Compound A": 3-(4-chloro-α-(4-(3- methylbenzyl)piperazinyl)benzyl)phenol;

"Compound B": 1-(bis(4-methoxyphenyl)methyl)-4-(2,3,4-trimethoxybenzyl)piperazine;

"Compound C": 1-(bis(4-fluorophenyl)methyl)-4-(3-(2,3,4- trimethoxyphenyl)-2-propen-1-yl)piperazine;

KB-2796: 1-bis(4-fluorophenyl)methyl)-4-(2,3,4- trimethoxybenzyl)piperazine;

Flumarizine: 1-(bis(4-fluorophenyl)methyl)-4-(3-phenyl-2- propen-1-yl)piperazine; and

Cinnarizine: 1-(diphenylmethyl)-4-(3-phenyl-2-propen-1- yl)piperazine.

6. None of the compounds disclosed in Iwamoto I or II, as identified in Paragraph 5 above, have any substituents attached to any of the carbon atoms in the piperazine ring.

7. I have collaborated on tests conducted on certain diphenylpiperazine compounds using the assay procedures set out in Example 92 on pages 156-157 of the specification of the Application. These tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II and identified in Paragraph 5 above, had no substituents on the carbon atoms of the piperazine ring. The other compound of the pair was the same as the first except that it had two methyl groups on the carbon atoms of the piperazine ring.

8. The compounds tested according to Paragraph 7 were as follows, wherein Compounds 1-4 have no substituents on the carbon atoms of the piperazine ring, and Compounds 1a-4a have two methyl groups on the carbon atoms of the piperazine ring:

Compound 1: (±)-3-(α-(4-Allyl-1-piperazinyl)-4- chlorobenzyl)phenol;

Compound 1a: (±)-3-((αR*)-α-((2S*,5R*)-4-Allyl-2,5- dimethyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 2: (±)-3-(α-(4-Allyl-1-piperazinyl)-4- bromobenzyl)phenol;

Compound 2a: (±)-3-((αR*)-α-((2S*,5R*)-4-Allyl-2,5- dimethyl-1-piperazinyl)-4-bromobenzyl)phenol;

Compound 3: (±)-3-(α-(4-Allyl-1- piperazinyl)benzyl)phenol;

Compound 3a: (±)-3-((αR*)-α-((2S*,5R*)-4-Allyl-2,5- dimethyl-1-piperazinyl)benzyl)phenol;

Compound 4: (±)-3-(α-(4-Methyl-1-piperazinyl)benzyl)phenol; and

Compound 4a: (±)-3-((αR*)-α-((2R*,5S*)-2,4,5-Trimethyl-1-piperazinyl)benzyl)phenol.

9. The test results for Compounds 1-4 and Compound 1a- 4a described in Paragraphs 7-8, using assays described in Example 92 on pages 156-157 of the specification of the Application, are as follows:

Compound	Mu Receptor IC50 (nM)	Mouse Vas Deferens ED50 (nM)	Delta Receptor IC50 (nM)
Compound 1	3500	2000	50
Compound 1a	90	40	15
Compound 2	2000	*	60
Compound 2a	200	100	80
Compound 3	200	nd	60
Compound 3a	25	78	1.3
Compound 4	700	nd	140
Compound 4a	1.6	46	38

nd = not determined

*Test results showed that Compound 2 has antagonistic activity rather than agonist activity in the mouse vas deferens assay

10. The test results listed in Paragraph 9 above show that substituted Compound 1a has fifty times more potency than unsubstituted Compound 1 according to the Mouse Vas Deferens ED50, more than thirty times more potency according to the Mu Receptor IC50, and more than three times more potency according to the Delta Receptor IC50. Substituted Compound 2a has ten times more potency than Compound 2 according to the Mu Receptor IC50. Substituted Compound 3a has more than 45 times more potency than unsubstituted Compound 3 according to the Delta Receptor IC50 and 8 times more potency according to the Mu Receptor IC50. Compound 4a has more than four hundred

times more potency than unsubstituted Compound 4 according to the Mu Receptor IC50 and more than three times more potency according to the Delta Receptor IC50.

11. The test results in Paragraphs 9 and 10 above comparing compounds in which the piperazine ring is substituted with two methyl groups on the carbon atoms with those that do not have a substituent on any of the carbon atoms of the piperazine ring show a general trend in which the substituted compounds have significantly greater opioid activity according to test results of assays described in Example 92 on pages 156-157 of the specification of the Application.

All statements made herein of my own knowledge are true, and all statements made on inference and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Robert Walton McNutt, Jr.

Dr. Robert Walton McNutt, Jr.

Date: February 7, 1996

APPENDIX C
RELATED PROCEEDINGS APPENDIX

None.

APPENDIX D
LIST OF REFERENCES RELIED ON BY EXAMINER

1) WO93/15062.

2) U.S. Pat. No. 5,658,908.

3) Bilsky, et al., "Characterization of Enantiomers of (±)BW373U86 and Related Compounds: Highly Selective Nonpeptidic Delta Opioid Agonists," *Reg. Peptides* 54:25-26(1994)—**Cited as C1 in Applicants' November 17, 2003 IDS.**

4) Bilsky, et al., "SNC 80, A Selective, Nonpeptidic and Systemically Active Opioid Delta Agonist," *J. Pharmacol. Exper. Therap.* 273:359-366 (1995)—**Cited as C2 in Applicants' November 17, 2003 IDS.**

5) Calderon, et al., "Probes for Narcotic Receptor Mediated Phenomena. 19. Synthesis of (+)-4-[(αR)-α-((2S,5R)-4-Allyl-2,5-Dimethyl-1-Piperazinyl)-3-Methoxybenzyl]-N,N-Diethylbenzamide (SNC 80): A Highly Selective, Nonpeptide Δ Opioid Receptor Agonist," *J. Med. Chem.* 37:2125-2128 (1994)—**Cited as C4 in Applicants' November 17, 2003 IDS.**

6) Calderon, et al., "Probes for Narcotic Receptor Mediated Phenomena. 23. Synthesis, Opioid Receptor Binding, and Bioassay of the Highly Selective δ Agonist (+)-4-[(αR)-α-((2S,5R)-4-Allyl-2,5-Dimethyl-1-Piperazinyl)-3-Methoxybenzyl]-N,N-Diethylbenzamide (SNC 80) and Related Novel Nonpeptide Δ Opioid Receptor Ligands," *J. Med. Chem.* 40:695-704 (1997)—**Cited as C5 in Applicants' November 17, 2003 IDS.**